

NASA TT F-13,729

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N72-10075 (NASA-TT-F-13729) INTEGRATISM: A PATH
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Unclas Engelhardt (Scripta Technica, Inc.) Oct.
08364 1971 28 p CSCI 06C G3/04

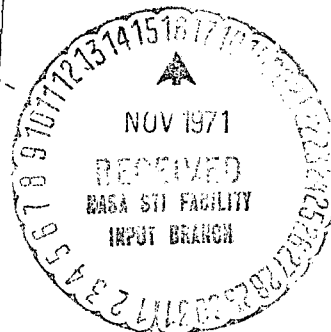
Translation of "Integratizm - put' ot prostogo k slozhnomu v poznanii
yavleniy zhizni"

In: Izvestiya, Akademii Nauk SSSR, Seriya Biologicheskaya, No. 6, Nov.-Dec.
1970, pp. 799-822.

FACILITY FORM 602

N72-10075
(ACCESSION NUMBER)
28
(PAGES)
✓
(NASA CR OR TMX OR AD NUMBER)

(THRU)
G3
(CODE)
04
(CATEGORY)



NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
WASHINGTON, D.C. 20546

OCTOBER 1971

INTEGRATISM—A PATH FROM THE SIMPLE TO THE COMPLEX IN UNDERSTANDING LIFE PHENOMENA*

V.A. Engelhardt

ABSTRACT: In modern theoretical biology two opposing trends are apparent—organicism and reductionism. Efforts are being made to overcome their contradictions and to achieve a synthesis of their ways of approach in tackling fundamental problems in the study of life.

The recent advances of molecular biology justify the opinion that increased attention should be paid to studies along the line which can be defined as integratism. Its objects is to elucidate the principles and mechanisms involved in the transition from the primitive and elementary level to levels of ever increasing degrees of complexity and organization; in other words to reverse the principle of reductionism. The basis of the transition from component parts to a new complex whole is the integration of elements of lower level into the entity of the next higher level of organization. It can be said that the aim of integratism is the understanding of the factors which make up the difference between the whole and the sum of its parts in the hierarchy of biological organization.

In the year when all progressive mankind celebrates the 100th anniversary of Lenin's birth, a great deal of attention is being devoted to the profound works of Lenin concerned with basic problems of natural science. Of primary importance here is the situation prevailing the field of physics during the time in which Lenin wrote his philosophical works. During the late 19th and early 20th century outlines of entirely new "neoclassical" concepts became apparent, which were

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*This article is based to a considerable extent on material from a paper read by V.A. Engelhardt and A.A. Baev on 1 April 1970 at a festive joint meeting of the Institute for Molecular Biology and the Institute of Chemistry of Natural Compounds, commemorating the 100th anniversary of the birth of V.I. Lenin. The text of this article includes that portion of the paper concerned with the significant role attributed to the study of the integration principle in understanding life phenomena.

**Numbers in the margin indicate pagination in the foreign text.

molded in a short period of time into a clear picture, requiring a revision of apparently immutable concepts of classical physics. A state of affairs came into being, containing elements of a crisis, since the foundations of physical concepts were shattered, as well as revolutionary elements marking the start of a new epoch if not the beginning of a new era. The deep thought of a thinker enabled Lenin to estimate correctly the mutual relations between the old and the new in the scientific understanding of the world, to foresee the course of the future development of man's concept of the surrounding world, and to describe the main features of the conceiving process itself, i.e., human thought. However, except for the last one of the aspects mentioned above, the main concern was to interpret laws and understand phenomena found in the surrounding world of nonliving nature, which was the only one considered by physics at that time. The study of the living world, of which we constitute a small part, was not subject at that time to such extensive perturbations as those characterizing the physical concept of the world. In biological investigations a descriptive approach predominated, which involved primarily a systematic recording of information and facts. At the same time, investigation of the living world, and first of all any attempt to answer the basic question—what is life—, confronts the investigator with tasks of an entirely new order. Finding correct approaches to the solution of these problems is a matter of primary importance. /800

In Lenin's works the particle of the living world known as man and his thinking process occupied an important place, rightfully assigned to him, but merely as a subject in his mutual interrelationships with the surrounding world, in a plane dealing with interpretation of the essence of thought and perception of nature, i.e., as an investigating, conceiving and receptive subject but not as an object of investigation.

At the beginning of the 20th century, when Lenin's sharp mind was aimed at problems of cognition, the principles involved in understanding the specific features of the living world still constituted a very narrow field of endeavour. From a gnoseological standpoint, the principal landmarks of biology at that time included Darwin's theory of evolution and the materialistic approach, based on Pavlov's works, to an understanding of phenomena of the higher nervous activity. Vitalism had already suffered devastating blows and was condemned to death. However, experimental opportunities allowing a deeper penetration into the specific features of objects found in living nature were still extremely limited; in biological investigations, the principles of recording (constatation) predominated to a great extent over interpretation, and the collection of analytic material, which could reflect the material foundations of biological functions, was proceeding at a slow pace.

In the biology field important events started to take place beginning approximately with the second half our century. The explosive process of rapid accumulation of experimental material was properly characterized as the beginning of a new era. It is fitting to mention once more the words spoken by the eminent physicist Blackett, President of the British Royal Society, namely that "molecular biology played the same revolutionary role in the science concerned with the living world as the quantum theory in nuclear physics forty years ago".

The biological revolution, in which all of us are witnesses and participants, has not only raised the study of basic biological problems to a qualitatively new

level, but precisely in views of its rapid development is confronting researchers in an ever growing measure with problems of a philosophical and gnoseological nature.

We are now confronted with a tremendous expansion of factual information covering most important aspects of the existence of the living world. The natural consequence of this fact in our days is a noticeably increasing attempt to effect a wider generalization of fundamental concepts touching upon basic approaches in studying life phenomena and aimed at the elaboration of scientific-cognitive principles, which take into account the specific character of living objects and of the varied manifestations of life activities. As a concrete expression of this trend we must consider the growing interest in problems of theoretical biology and, specifically, in philosophical aspects of the approach to these problems.

Thus, a special "Journal of Theoretical Biology" has already been published several years. In the USSR, collective works entitled "Problems of biophysics and theoretical biology" are being published at Tbilisi University. It is true that these publications still contain predominantly works concerned with a formulation of theoretical concepts dealing with certain particular biological problems. Questions of a wide scientific-cognitive nature are still discussed to a limited extent in these publications. This deficiency is remedied to a significant extent by a considerable number of scientific meetings, conferences and symposia devoted to problems mentioned above.

As a good illustration of the above statements we can cite two symposia conducted under the auspices of the International Congress of Biological Sciences and under the chairmanship of the eminent biologist Waddington and the slogan: "On the path to theoretical biology" (Waddington, 1968). The volume containing papers given at the first symposium has been translated into Russian, and the second volume is in press. The following titles of reports discussed at these symposia give an idea of the purpose of such scientific meetings: "Fundamental biological concepts"; "Causes and consequences in biology" (the problem of determinism, an important philosophical concept); "An attempt to build a scheme of a primary organism"; "On the path to a physical theory of self-organization", etc. /801

A sign of the times is the fact that representatives of sometimes widely remote fields of activity or protagonists of sharply opposed concepts and viewpoints gather together at these scientific meetings, sometimes even sharing the same discussion round-table. Also characteristic is the varied professional background of the members and the great variety of the basic concepts examined at these meetings. We must note the high scientific level of analysis of the problems discussed, their contemporary character and the way they are aimed at the most basic foundations of the biological world outlook. All these facts are convincing proof of the fact that the biological revolution, under whose banner modern experimental investigations are being carried out at a rapidly growing rate, is characterized not only by an avalanche-like (and sometimes even explosive) process of factual data collection and by stunning breakthroughs in our knowledge of areas which recently still seemed to be inaccessible or infinitely remote to our understanding. At the same time, the need to find integrative principles which would allow to lay the groundwork of fundamental concepts is becoming more and more

apparent. At present, the most urgent problem for science as a whole involves the finding of an optimal synthesis of two dominating trends, namely differentiation and integration. The same necessity is also acutely apparent within the limits of our particular field of knowledge, i.e. the study of the living world.

There is a considerable number of biological problems awaiting a theoretical understanding and a philosophical interpretation. No doubt the most basic problem of this kind is the question of the competence in reducing the complex phenomena encountered in biology to elementary levels of physics and chemistry. This is a fundamental gnoseological problem, and in this case difficulties are compounded by the fact that subject to "reduction" is the most complex, the finest and the most perfect of all things known to us on our planet, namely life phenomena. And we want to reduce them to the most simple things we know, i.e., to the behavior and properties of molecules.

In this connection sharp and violent arguments have been raging in the recent past. Unwillingly we are reminded of the violent antagonism which flared up in the biochemistry faculty, on the one hand, the metabolism faculty, on the other, at the Leningrad University. The former was represented by the author of this article, a rather youthful scientist at that time, while the latter was represented by the prominent late Professor E.S. London.

I recall the contempt in which London held us, calling us "test tube scientists" and violently refuting any value whatsoever of our miserable "test tube" experiments. In place of these tests, London struck the imagination of his students with his results of a chemical analysis of blood samples collected on an intact animal from "vascular fistulas" developed by him. Blood flowing into the heart and out of it was investigated and compared, and on the basis of two figures "more-less" an estimate was made on the entire highly complex aggregate of processes constituting the metabolism of living tissues and organs. We must admit that history has dealt harshly with this heritage which disappeared without a trace.

In our scientific circles the problem of reducibility, i.e. whether it is admissible to explain the properties of a complex thing by studying its most simple parts, was at one time considered as a most harmful heresy. For little competent "authorities", claiming to be apostles of an infallable faith, the favorite argument was the canonized dogma asserting that efforts to reduce, for example, phenomena of heredity to the action of genes are simply futile, if not downright criminal. The fallacious character of any efforts to reduce complex phenomena to simple ones was so firmly asserted that this viewpoint permeated all fields of investigation of living objects.

The reduction principle suffered, in this connection, the same fate as such fundamental concepts of contemporary natural science like the theory of relativity, chemical resonance, Mendel's and Morgan's theory, cybernetics, and the chromosome theory of heredity.

At present, the problem of "reduction", which in the 1920's and 30's engaged the diligent efforts of our latter-day "philosophers", who had little knowledge of science and whose minds were aimed at the established order, must essentially

be reconsidered from head to toe. All arguments concerning the competence of reduction as the basic way of studying complex phenomena, and primarily in the domain of the living world, have been stopped completely by the entire course of actual progress achieved in scientific research. No sensible person today will question the fact that molecular biology constitutes the basis for a knowledge of the living world, in the same way as the physics of elementary particles lays the foundation for a knowledge of the laws of nature in a broader, all-encompassing aspect.

At present only the question of a correct relationship between two trends of scientific thought in studying the living world is being discussed in biological circles. These trends are known as "reductionism" and "organicism". A symposium devoted to this topic was organized 2 years ago (Koestler, 1969). Some problems discussed at this symposium will be examined later in this article. Coming back to what we have just been saying, it must be underscored that the problem of "reducibility" is at present turned around in a diametrically opposite direction. The question of major importance is the following: how does the complex arise out of the simple, what forces enter into action, what are the laws governing this process, how are new properties created as a result of growing complexity, with a transition to new and higher levels of organization? Many of these pertinent questions are discussed in various books published in recent years in our country. Thus, we can cite the books of V.I. Kremyansky "Structural levels of living matter", the previously mentioned volume "On the path to theoretical biology", the proceedings of the symposium "Self-organizing systems", the book by I.V. Blauberg, V.N. Sadovsky and E.G. Yudin "Systemic approach: premises, problems, difficulties", etc.

We shall not examine here the historical stages in the development and struggle of those concepts which will be discussed here, and it is sufficient to proceed directly from the present state of affairs as a starting point. This state of affairs is determined by two trends which have existed for a long time in the study of the living world and which even today are opposed to each in a correspondingly modified form.

These trends, as was mentioned above, are designated by the commonly used terms "reductionism" and "organicism". These terms are sufficiently clear by themselves, and we shall merely give a few brief comments. Reductionism designates a research principle based on the conviction that the path to a knowledge of the complex consists in breaking down this complex into more and more simple components and in studying their nature and properties. It is assumed that, by reducing the complex to the totality or sum of its parts, we, after studying the latter, shall also obtain some information on the properties of the original whole.

In contrast, organicism postulates in advance the impossibility of reducing the complex to the simple and accepts, as the object of its investigation, only one or another level of the complex integrity or that level of organization which is adequate to the character of the studied functions and properties.

The positions taken by organicism are based on a postulate, whose formulation is ascribed by some people already to Plato, and according to which the whole is something bigger than the simple sum of its parts. In a half-joking form this thought was expressed at one of the above-mentioned symposia by

L. Bertalanffi, one of the most eminent modern biologists, having a marked inclination towards theoretical aspects. He said: "If we know everything about 'one', and knowing that one and one equals two, we still do not know everything about 'two', since a certain 'and' is added here and we must know what is introduced by this element 'and'".

This may sound funny, but there are good reasons to assume that a search for precisely this "And" will constitute the object of considerable efforts in the future period of development of biological research, starting from precisely those lowest molecular levels in which we have witnessed the most stunning successes.

Reductionism at present does not need any kind of defense or arguments to prove its competence. Such proofs are given by the sum total of modern biological research, which in essence is simply a triumphal parade of the reductionist principle. Molecular biology is a direct child of reductionism, and is responsible for all the epoch-making successes and achievements making up the substance of our modern biological revolution.

Naturally it would be wrong to assume that reductionism, as a methodological base of biological research, claims an exclusive role in the study of the living world. Organicism still retains its own and sufficiently broad area of research, and our present task must consist to a large extent not in an opposition of these two methodological approaches, but rather in finding ways to effect their synthesis or at least their mutual supplementation, to find certain complementary forms, i.e. this interrelationship of parts in a complex whole, which Bohr propounded with particular insistence as a leading principle in our present picture of the universe, a principle capable of reaching the greatest depths and possessing an especially broad character of universality.

As testimony of the fact that protagonists of organicism themselves are aware of the need to find correct forms of interrelationship between these two approaches to the study of life phenomena and that efforts to reach this goal are under way, we can mention the symposium held in Alpbach in 1968, organized by Alfred Koestler (Koestler, 1969) author of a number of books dealing with problems of modern natural science. Proceedings of this symposium were published under the significant title: "Beyond reductionism".

We must assume that by using this title the organizers of the symposium wanted to underscore that they are far from rejecting reductionism and want to find ways to achieve forward progress.

A rather extensive journal article by W. Thorpe (Thorpe, 1969), describing the results of works reported at this symposium, was published under the title: "Reductionism versus organicism". In this article, the author, although clearly attracted to organicism, is forced to admit the great superiority of the brilliant achievements scored by reductionism. While not hesitating to call reductionism "our present-day nihilism" (by the way, providing no basis whatsoever for this very paradoxical statement), the author of this article nevertheless reaches the significant conclusion that all our hopes to successfully disclose the secrets of living nature, manifesting themselves at higher levels of organization, must rest on "an attack from the bottom", i.e. precisely from those lower levels in which the so-called "reductionist" molecular biology is operating.

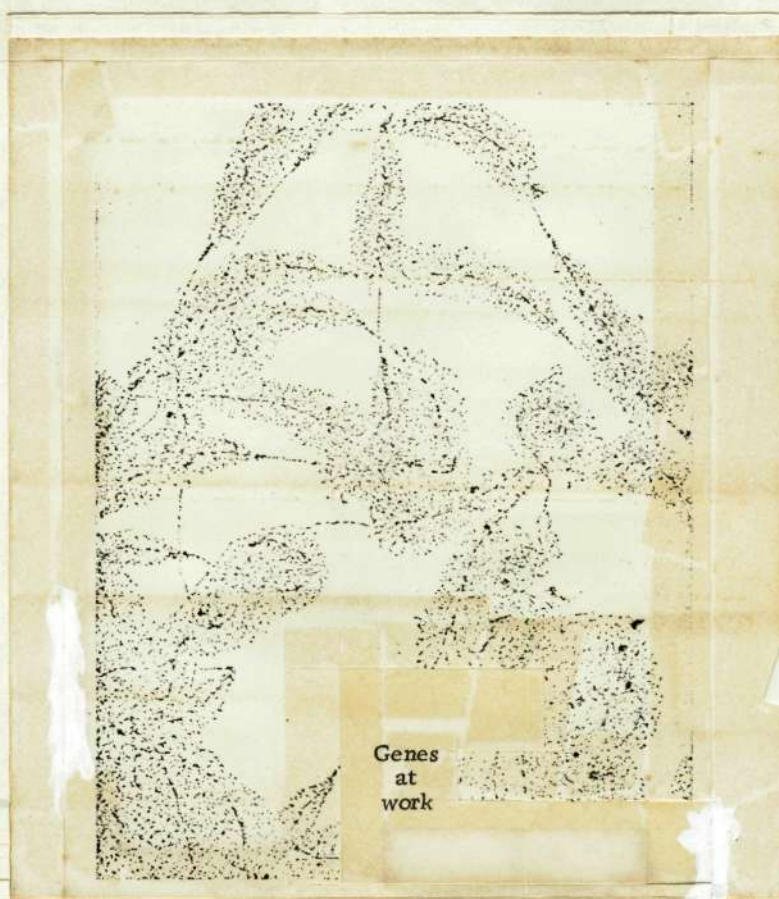


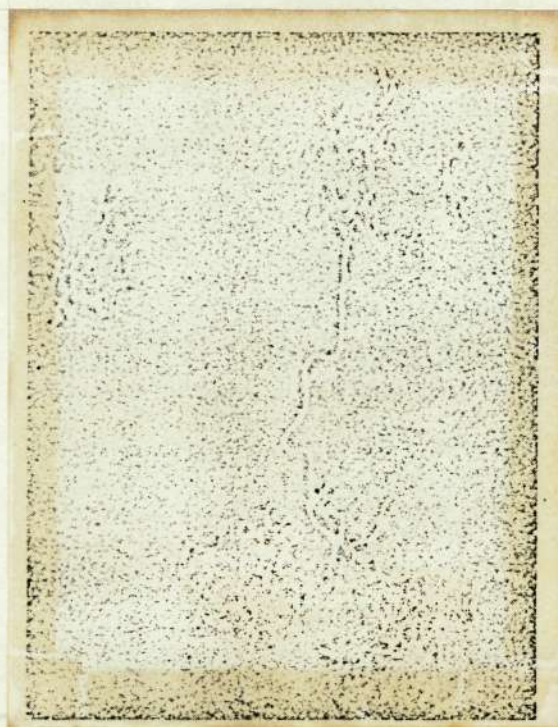
Figure 1. Consecutive Growth of RNA Strands Reproducing Genes Recorded in the DNA Structure.

So that we do not return any more to this opposition of reductionism and organicism, it may be useful to cite a statement of great depth and insight made by I. P. Pavlov, the greatest proponent of organicism of our century. In a speech devoted to Haidenhain, eminent physiologist of the late 19th century, Pavlov (1949) describes him as "a representative of that physiology which must replace our contemporary organic physiology and which can be considered as the forerunner of the last stage in the science of life, namely the physiology of the living molecule". /804

Reductionism has firmly gained a dominant position among other means of investigation of the living world. This dominant position is indisputably strengthened by brilliant achievements which are unequalled in most other areas of natural science. If we want to formulate the most characteristic feature of molecular biology we could say that its task consists in studying life phenomena by operating with nonliving objects, i.e. objects devoid of life.

The successes achieved in molecular biology by following the path of reductionism are too numerous and at the same time sufficiently well known to enumerate them all at this point. For the purposes of this study we shall only mention two examples from the most recent past.

Using with great skill modern electron-microscope techniques, Miller and Beatty (1969) were able to demonstrate visibly the first stage in the functioning of a gene, a process of so-called transcription, by means of which the synthesis



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Figure 2. Isolated Group of 3 Genes Effecting the Conversion of Lactose (Milk Sugar).

of RNA molecules takes place under the action of RNA polymerase in a DNA section corresponding to one gene (Fig. 1). Strands of the RNA being synthesized, the length of which increases consecutively, can be seen in the electron micro-
 photograph. Up to 100 molecules of RNA polymerase exert their effect in one DNA section, and the manner in which the consecutive (progressive) growth of RNA molecules takes place can be seen in the photograph. This is like a picture, fixed on the cross-section by a time coordinate, of the dynamics of biosynthesis of a nucleic acid, a picture of a "gene at work".

/805

Figure 2, taken from the work of Shapiro et al. (1969), shows a group of 3 functionally bound genes isolated from the hereditary apparatus (genome) of *Bacterium coli*. In this photograph, the middle rectilinear sector represents the segment of the DNA polynucleotide chain containing these genes. Along the ends of this segment we can see the neighboring parts of the DNA chain, twisted into an irregular bundle, which can be removed by careful action of corresponding enzymes.

Thus, as a result a refined experimental technique, genes, the existence of which were appraised until recently to a considerable extent according to the effects of their action, can now be directly perceived by us and can be isolated and subjected to analysis like a chemical entity. It should be mentioned at this point that work on the synthesis of genes has progressed to a far-reaching point.

Probably within a short period of time, by using principles of holography and electron microscopy, we shall be able to observe such a gene in a three-dimensional relief form, and we shall almost tangibly be able to perceive all the details of its structure.

Such are some of the visibly perceived illustrations of those boundaries reached by contemporary reductionism. However, no matter how great are the successes achieved in this field, it would be wrong to think that the achievements of reductionism should be considered as an end in itself, as a final stage which does not result in further research. First, the area of application of the principles of reductionism will constantly expand and speaking practically, we must consider that its tasks are inexhaustible to the same extent as Lenin in his time had prophetically stated that the study of atoms or electrons is inexhaustible. As we shall point out later, it is conceivable that a transition can be made from the present molecular level to a still lower level, lying in the sphere of atoms and then even of electron structures. This is, so to speak, an extension of reductionism into further, lower-lying areas.

Another methodological significance, entirely different in principle, must be ascribed to such an orientation in scientific research which, from the most primitive, elementary and mainly molecular levels, where present-day reductionism plays a dominant role, would lead into an opposite direction, namely towards levels of increasing complexity of organization, to systems acquiring new properties and functions. This is a direction or trend, the task of which must be to overcome the one-sided (unilateral) nature of reductionism.

/806

The fundamental nature of this trend consists in finding a method of including and integrating more primitive elements into a new whole (integrity) standing on a higher level of the organizational hierarchy and having different degrees of order. The main feature in this transition from the simple to the complex is precisely its integrative character, the formation of a definite system of connections (bonds), the loss by components of the newly-formed whole of a certain portion of their individual properties and their absorption by properties of the integral whole. Accordingly, we suggest the term integratism to designate this particular scientific cognitive trend.

Before we examined the main features of this path it is appropriate to make several remarks in regard to the fact as to whether the present predominant level of biological research, i.e. the molecular level, can be considered as the ultimate boundary of reductionism. There is no doubt that this boundary will be preserved for a long time and that the molecular level will remain the main arena for the development of further important events in our knowledge of life phenomena.

However, we must be aware of the fact that trends in scientific research to switch to even lower levels, mainly to the level of electronic phenomena, will assume an ever growing significance. Signs of such a transition are already clearly apparent and can be seen, for example, in books whose titles reflect an attempt of the authors to interpret life phenomena not as concepts of molecular properties and interactions, but rather as a transition to even lower forms of organization. Thus, for example, Szent Gyorgyi (1969) has published a book entitled "Introduction to Submolecular biology", and publication of a book entitled "Bioelectronics" by the same author has been reported. Knowing the tendency of the author of these works to indulge in light, although effective and alluring, hypotheses and categorical statements, it is hard to consider these publications as an impressive argument confirming the significance of this new research trend. However, statements have been made by scientists of considerably greater authority, which support the above viewpoint. Thus, John Bernal (1969) in his latest book,

gives the following definition of life: "Life is a partial, continuous, progressing and varied self-realization, interacting with the environment, of potential capabilities of atomic electron states".

As a matter of fact, if life is interpreted this way we can naturally conclude that in our efforts to learn more about the phenomena and essence of life we must expect the necessity of switching over in the future to a study of precisely the atomic and electronic levels. In some individual and particular cases, we are already working at these levels at the present time.

We can leave aside the field of electron microscopy, where an electron bundle is used as a tool and is not a subject of investigation. Another powerful tool of modern experimentation, namely X-ray diffraction analysis, already brings us closer to the level of electronic structures of biopolymers, since the investigator is concerned here with charts of electron densities, describing the location of separate atoms in the molecules of substances important in life, primarily proteins. Here, strictly speaking, we are already gaining access to levels located below the molecular level, but the data obtained are used to reconstruct the three-dimensional structure of a macro-molecule, i.e. we are returning again to the same molecular level. We can state that here a bridge seems to span two very important levels and the information obtained constitutes a substantial base for the elucidation of the role played by electron states of molecules in their biological properties and function. It is precisely this trend which is now undergoing development, for example, in the extensive research work carried out by Pullmann at the Paris Institute of Physical and Chemical Biology.

/807

Obviously, research at the electronic level will play a substantial role in the study of those electronic mechanisms which take part in all phenomena involving the energy of biological systems. However, this refers to an area which we shall not examine at all in this article.

Having embarked on a course of predictions or prophecies (which, by the way, are now designated by the more respectable word "prognoses"), we can assume that the electronic level in research will also play a very important role in the area which constitutes the principal object of our present investigation, namely a knowledge of the motive forces stipulating the phenomena and principles of integratism mentioned above.

What then is the content of the concept "integratism"?

To answer this question let us return to the same central point concerning the mutual relationship between the part and the whole, the complex and the simple. This is one of the important philosophical problems dealing with the theory of knowledge (cognition), which confronted thinkers since the days of antiquity.

We would get lost in a dense scholastic maze if we were to attempt to understand the meaning of such concepts as order, system, organization, whole, structure, element; to these we should also add the concept of information. Even specialists in the field of philosophic problems (see Blauberg et al., 1969) admit that these concepts suffer from "multiplicity of meaning in their usage", and that "it is very difficult at present in scientific practice" to define them in an unambiguous and comprehensive manner". Therefore, without getting into fine points

of semantics, these terms will be used here in a somewhat simplified sense, since the fundamental concepts and conclusions discussed here do not require a thorough and detailed analysis of the content of the concepts.

Mutual relations between the part and the whole are characterized first of all by the presence of definite and firmly established forms of interaction between the parts making up the whole; these are actions possessing the character of bonds. Without the presence of bonds between the parts no whole of any kind could exist, since it would inevitably fall apart.

From the above statements we can draw the following conclusion: the difference between the whole and the sum of its parts consists in the presence of a system of bonds between the parts. It is precisely those bonds which constitute that new and hidden item which makes the whole different from the sum of its parts. These bonds represent that "and" mentioned in Bertalanffi's joking formulation cited above. That something which could be found in the composition of the whole, if it did not form bonds with the other parts, would be a foreign body and not a part of the whole.

The presence of a bond system during the formation of a whole from its free and scattered parts must be considered as the most basic and primary condition of integration, which is indispensable for the formation of a new whole. Whether this condition is sufficient in order that the aggregate formed may acquire the properties of a whole, this is a special question which will not be examined here.

The formation of a network of reciprocal bonds between the parts present in the emerging whole is a condition for the formation of this whole. And what are the consequences of the formation of these bonds, which consolidate a multiplicity into a unity? These consequences affect both the parts and the whole, since the formation of new bonds results in definite changes of properties. A part, by entering into the composition of a new and more complex unity, loses some of its properties as if sacrificing them for the sake of newly acquired advantages, such as, for example, a reduction in free energy of the system. The properties of the part are eradicated to a certain extent, are absorbed by the properties of the whole and are transformed into its properties. On the other hand, the emergence of a new whole is accompanied by the appearance in this whole of new properties, which are by no means identical with those "lost" by the component part, but are rather determined mainly by precisely those bonds which originated when the part entered into the emerging whole;

/808

We have three elements, the sum total of which characterizes the mutual relations between the whole and the part: 1) formation of an interacting system of bonds between the parts making up the whole; 2) loss of certain properties of the part when it enters into the composition of the whole; 3) appearance in the emerging new whole of new properties, stipulated both by the properties of the component parts and the formation of new systems of bonds between parts. In addition, the parts are ordered and their spatial and functional interrelations are determined.

To explain what has been said above by means of the most simple example, let us consider the formation of glycogen from glucose. By becoming part of

glycogen glucose loses its reduction properties and mobility, namely its diffusion ability. The whole (integrity) of a higher order which has been formed, namely glycogen, has a high molecular weight, does not diffuse and acquires properties which allow it to perform the role of a reserve carbohydrate.

The result of the above sum total of events making up the whole is the fact that a part, which was previously an independent factor, becomes a component of an integral whole, which is consolidated internally. This result is designated by us precisely by the term "integration". Something which existed before ceases to exist as such and something new arises, which previously did not exist and which has new properties peculiar only to it.

An understanding of the essence of integration phenomena, of the rules, motive forces and sources of integration constitutes the main road which must be followed in order to elucidate the nature of biological organization at all its levels, starting from the lowest molecular levels and in the entire hierarchy of ever increasing degree of complexity. There is hardly any doubt that progress along this path must follow the line from the simple to the complex. This is precisely the path designated above under the term "integratism". The task to be accomplished in this direction involves the transition from reductionism, based on a breakdown of complex phenomena and a study of its most simple components, to an understanding of the rules governing biological organization. This fact was expressed in a successful, although somewhat paradoxical form, by A.A. Baev who stated that "integratism simply represents a movement directed forward (from reductionism) which involves stepping in a reverse direction".

An immutable fact is that integratism must grow from reductionism, using the results obtained by the latter as a starting point. At the same time we must realize that the path from the simple to the complex is much more difficult to follow than the path from the complex to the simple, i.e. the path which constitutes the basis of reductionism. However, we should not by any means consider this difficulty as unsurmountable. On the contrary, the reality of this path is convincingly confirmed by the continuous growth of data obtained in the course of extensive experimental investigations carried out in recent years. In order that the statements made here should not appear as purely speculative and unsubstantiated, we shall give further in this article a number of concrete illustrations of the manifold forms of expression and utilization of the principles of "integratism", which are already available to science.

It is necessary, however, to examine first certain considerations of a more general and basic character.

Along with the term "integratism" it is advisable to use the concept of integrative information as a guiding factor at all levels of integration. /809

The concept of information has introduced an entirely new and essentially specific category into the sphere of the cognitive complex used by us as a tool in the study of live objects and systems. Some authors even go as far as believing that "science has added information to such "atoms" of the universe as matter and energy" (Blauberg et al., 1969).

The concept of integrative information shall be used here to include the sum total of those properties which are necessary to ensure the possibility of an

integration in each individual case. These properties include first those which make it possible for a part that enters into the composition of a new whole to interact with other components of this whole. Interaction in this case presupposes that bonds are formed, and bonds presuppose that certain forces are present. Thus, we come to the conclusion that integrative information is made up of the sum total of those properties which ensure the presence of forces between intercomponent bonds. The integration process itself in that case consists in the manifestation of the action of these forces. The principal task of integratism then involves an understanding of the nature of forces taking part in integrative information, of the rules governing the action of these forces, of the sources from which they arise, of their location in space, etc.

The concept of integration is inseparably linked with the idea that a systemic principle must be present, since every whole is built on a system of bonds. At present, particularly great attention is being given to the study of laws governing the properties and behavior of systems. It is not by chance that the concept "systems theory" itself was formulated by the eminent theoretical biologist L. Bertalanffi. Principles based on a systems approach assume an exceptional significance in understanding the living world. It will be no surprise if the systems theory in the near future will play the same important role as did the information theory.

In the case of integration we are always confronted with an increase in order. Integration can quite successfully take place in a closed system. It would seem that the increase in order which occurs in this case enters into conflict with the second principle of thermodynamics, since the entropy of the system appears to decrease. Actually, this contradiction is purely apparent: integration strictly follows the direction of a decrease in the free energy of the system, and this decrease is always incomparably more significant than the negentropy of the increasing order. Let us take the most simple example, namely Plato's well-known experiment: if we consider two immiscible fluids of the same density, the fluid present in a smaller amount tends to assume a spherical shape. A sphere, however, is an infinitely more ordered system than the same mass of fluid which freely changes its shape under the action of random forces of the thermal motion of its molecules! We can explain this fact in a very simple manner: the sphere has a minimum surface at the given volume. Consequently, surface tension forces will exert their effect in this minimum and the gain in its free energy greatly exceeds the negentropy of the limitation of the freedom of movement of the molecules.

In view of the fact that this question is of basic significance, it is a good idea to mention one more experiment as an illustration of the actual state of affairs. A description of this experiment is borrowed from Foerster (1964). This experiment may seem naive in view of its simplicity, but it clearly demonstrates what we are talking about. Two sets of small cubes placed in two transparent drawers are at first arranged in a completely disorderly manner. Upon moving and shaking one of the drawers the disorderly arrangement of the cubes is preserved. However, if the second drawer is subjected to the same treatment, we can see that the cubes are arranged in a very orderly way and are lined up in rows. We can easily guess what has happened: the cubes in the second drawer have magnets attached to their sides. The tendency on the part of magnets of opposite charge to

/810

adhere to each other, thereby reducing the free energy of the system, greatly exceeds the negentropy of their orderliness. We can also see in this case that there is no violation of the second principle of thermodynamics.

The most simple case of integration can be found in reactions involving the biosynthesis of polymer molecules from monomers (the term "protomer", suggested by J. Monod, will be used further to designate the components entering into the composition of the new whole as a result of integration. Here, the situation is extremely simple. Integration is achieved as a result of the formation of main-valence bonds; consequently, integrative information in this case is primarily concentrated in those protomer groups which take part in the formation of the above-mentioned bonds. In addition, certain other factors may also play a role, for example, steric configuration, but these factors are of secondary importance. The previously mentioned formation of glycogen from glucose residues can serve as an example of this type of integration.

The participation of main-valence forces of chemical affinity in phenomena concerned with biological integration is primarily limited only by processes involving the formation of biopolymers. In practically all other cases, so-called weak forces of intermolecular reactions play a dominant role in integration. It is precisely these forces that we must consider as a factor of decisive importance in phenomena involving integration.

Forces of main-valence affinity have, in principle, a single character, which is determined by the electron structure of atoms taking part in the formation of such bonds. The latter possess considerable strength. In contrast, forces of intermolecular reactions exhibit a wide variety of forms, are considerably more mobile, are affected to a considerable extent by their environment, and frequently exhibit cooperation properties. Such forces include hydrogen bonds, electrostatic forces, Van der Waals-London forces, dipole-dipole interactions, dispersion forces, forces associated with charge transfer, etc. It must be stated that these forces in many respects are defined to a much lesser extent than main-valence forces of affinity, and that a great deal of attention is being devoted to their study at the present time. However, their nature and detailed information on their properties are of no interest to us now, and we shall limit ourselves to a simple enumeration of these forces; they are important to us because it is precisely those forces which are predominantly the carriers of the integrative information we are concerned with.

We must point out that in the case of integration based on main-valence bonds, which is the foundation of processes involving the synthesis of biopolymers, simple conditions are found only in the formation of high-molecular polysaccharides. Here, the information controlling the integration process is contained in the protomers proper, i.e. in the monosaccharide molecules. No external factors whatsoever, supplying information, take part in the process; enzymes do not supply information, but merely increase the reactivity of molecules. Different conditions are found in the biosynthesis of proteins and nucleic acids. In this case, we are dealing with a matrix mechanism, and it is not necessary to describe the nature of this mechanism since its main features are no doubt familiar to all. In the formation of colloidal polysaccharides, the integration of protomers could take place at the expense of the information contained in their molecules.

Such a type of information can be called endogenous or immanent, i.e. internally inherent in the protomer being integrated. This type of information is not sufficient for the creation of new wholes (integrities) with such a degree of complexity and such strict order as are found in protein macromolecules or nucleic acids. In order to solve this problem, the mechanism of matrix synthesis goes into action; it supplies from the outside information which determines the order and sequence of integration of protomers. The matrix itself, containing this information in the form of a chemical structural recording, in the order of arrangement of the nucleotides, does not enter into the composition of the final product formed under the guiding action of the matrix: "The Maur has done his job and he can leave". This is an exogenous type of integrative information (it could also be called a directing, guiding type). /811

The part played by the matrix mechanism makes it possible to solve perhaps one of the most complex problems of biological integration. Out of the utter thermodynamic disorder and the chaos represented by the motley mixture of different protomers, namely four or five nucleotides, on the one hand, and two dozen amino acids, on the other, a strictly prescribed and indissolvably maintained order must be achieved in the sequence of the mutual combination of the integrated elements, as well as a consolidation of these elements into a higher-level system, i.e. into the chemical structure of a molecule of the corresponding polymer, consisting of several hundred to several hundred thousand separate links.

We do not know to what extent such mechanisms, supplying integrative information from the outside, i.e. mechanisms of an exogenous type, take part at other levels of the hierarchic gradation of biological systems. Of course, our thoughts are directed unwittingly to the highest levels of this hierarchy, such as the mechanisms involved in memory or other functions of the nervous system. We believe, however, that it would be extremely light-headed on our part to count on the possibility of understanding the nature of integration phenomena at such high levels of biological organization. There is only one rational course, based on reason, which we must follow here. It is the long path leading from the levels of present-day reductionism to systems of increasing complexity. This path may seem to be immeasurably long if the organisms of a higher animal are considered as the final goal. However, let us remember that the path leading to the chemical synthesis of a protein molecule, to the synthesis of an enzyme or a gene, or to the visual observation of an isolated gene, the carrier of hereditary properties, appeared to us just as long at the start of this century!

Even if we realize that the road lying ahead of integratism is a long and difficult one, we can still get a large dose of optimism by surveying that stretch of the road which has already been covered. This stretch is considerable, and on the basis of the knowledge already acquired we can be assured that our planned course of research is correct and well-founded. Already at the present time, on hand of many examples, we can observe, so to speak, "integratism in action". To avoid any reproaches for making declarative statements, we feel that it is appropriate to recall some successes scored by integratism.

The effect of integration manifests itself in that the emerging new whole possesses certain quality factors which were not found in the protomers included into its composition, but which are definitely predetermined by their properties.

The most simple and highly important examples of this fact are already available to us at the very early stages of the growing complexity of biological formations, namely in processes involving the buildup of biopolymer molecules.

We have already mentioned the role played by matrix synthesis as a mechanism ensuring the supply of exogenous integrative information during formation of the main-valence framework of the macromolecules. It is remarkable that the primary product of integration, namely the newly formed linear, i.e. one-dimensional, structure expressed in the sequence of arrangement of protomers, amino acids or nucleotides, now contains a new type of conformational information which predetermines a strictly prescribed three-dimensional space arrangement of parts of the molecule. This can be considered as an integration of a special character, taking place not as a result of the inclusion of new components into the system, but rather as a result of the determined mutual arrangement of parts of the system in three-dimensional space. At present, extensive information along these lines is available both for proteins and nucleic acids. /812

Characteristic for the protein molecule is the formation of alpha-helices, or folded structures, postulated by L. Pauling; then, the polypeptide chain with such a secondary structure undergoes a further reconstruction in space, resulting in the formation of a tertiary structure. Thus, an element having a single dimension, i.e. a polypeptide chain of linear structure, is transformed into a three-dimensional body having a strictly determined shape, and not into a disorderedly bundle which we would have obtained by crumpling a thread. By what factor is this shape prescribed, what kind of integrative information determines its outline? The answer to these questions is known precisely: the tertiary spatial structure is uniquely defined and is determined by the primary chemical structure of the peptide chain, i.e. by the nature and order of arrangement of amino acid residues in this chain.

A fact of primary importance is that the three-dimensional structure of the protein molecule, formed on the basis of the information present in the primary structure, in turn contains information of an entirely new type, namely functional information: this structure exerts a decisive effect on the properties of the protein molecule, including its most important biological properties, such as, for example, on the ability of hemoglobin to react with oxygen or on the catalytic properties of enzymes.

In regard to another group of biopolymers, namely nucleic acids, the information available to us is not as extensive from the standpoint of the number of investigated objects, but nevertheless is definite enough to enable us to make some positive deductions and conclusions. Investigations of low-molecular nucleic acids, performing mainly transfer functions (t-RNA), have established that many of these compounds have a primary structure. Study of a number of chemical and physical properties has shown the presence of a secondary structure which could be represented schematically in two dimensions, i.e. in a plane, in the form of a so-called "clover leaf" (Fig. 3). By combining the results of an X-ray diffraction analysis (still rather scarce at present) with certain data on various parameters (hydrodynamic properties, isotope exchange, possible hydrophobic interactions, etc.) it was possible to construct a three-dimensional model of the molecule (Fig. 4) (Levt, 1969).

It can be assumed that the basic rules governing the transition from a one-dimensional structure to a spatial, three-dimensional structure are identical for both proteins and nucleic acids. In the first stage, during formation of the polymer chain, integrative information was supplied by forces of main-valence affinity. In the following stage of integration examined by us above, namely the conformation stage, the forces of weak interactions mentioned above enter into the picture. In this case, these forces exert their effect within the limits of a single molecule, determining the spatial conformation (configuration) of the latter and imparting to the emerging system new properties of a chemical and physical nature, and thereby also of a biological nature.

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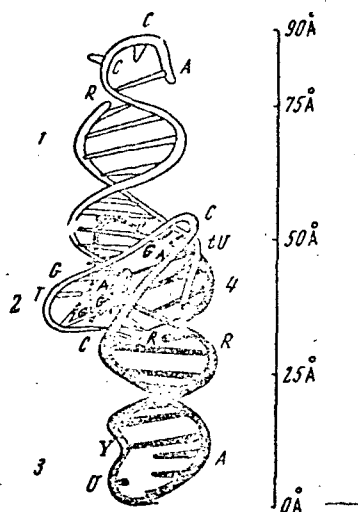


Figure 4. Schematic Three-Dimensional Structure of t-RNA: 1) Acceptor Branch; 2) Thimidyl Branch; 3) Anticodon Branch; 4) Dihydrouridyl Branch

molecules of certain substances, for example certain products of intracellular metabolism, i.e., so-called metabolites, or certain hormones, etc., may cause changes in conformations, accompanied by changes in functional properties of a given protein. Here, a many-sided connection takes place between different systems, i.e., entirely new integrative interrelations are established, which already encompass considerably broader areas of biological organization.

We have examined integration phenomena taking place at the level where biopolymer macromolecules are built up and where these molecules undergo conformational changes, i.e., within the limits of a single molecule, these phenomena cover a range extending from the primary chemical structure to the tertiary structure. The next level of increasing complexity includes polymolecular systems; in the formation of such systems integration takes place on the basis of association phenomena,

i.e., as a result of intermolecular reactions. As the transition, known long ago, to classical phenomena of polymolecular associations we can rightfully consider the peculiar phenomenon of directed (guided) association, which has been discovered recently at our Institute during investigations carried out in the laboratory of A.A. Baev in collaboration with A. Mirzabekov.

These phenomena consists in the fact that if macromolecules (we have in mind transfer (t-RNA) molecules) are broken down or "cut" into a certain number of large fragments by means of a strictly controlled enzymic action, then these fragments, taken separately, show a total loss of their characteristic biological function, namely the ability to bind the corresponding amino acid. However, if these fragments are mixed, the mixture again acquires, under favorable conditions its specific biological properties (Fig. 5). This has been shown on half portions of a molecule and even on smaller fragments, for example on quarter portions of a molecule (Mirzabekov et al., 1970).

/814

Clearly, we could not speak here of a true restoration of the original molecule: the main-valence bonds split by the action of the enzyme could not be arbitrarily restored. The problem can be reduced to the fact that the fragments acting as protomers are mutually associated under the effect of forces of intermolecular reactions and assemble together (self-assembly) to form an association complex, which reproduces the structure of the original molecule to such a full extent that it can be "recognized" by the enzyme which acts as a catalyst in the reaction involving the binding of an amino acid.

This phenomenon is of great interest to the problem of laws governing integrative information, which we are studying here. We were dealing with a complex whole, namely a nucleic acid macromolecule. In order to perform its functions,

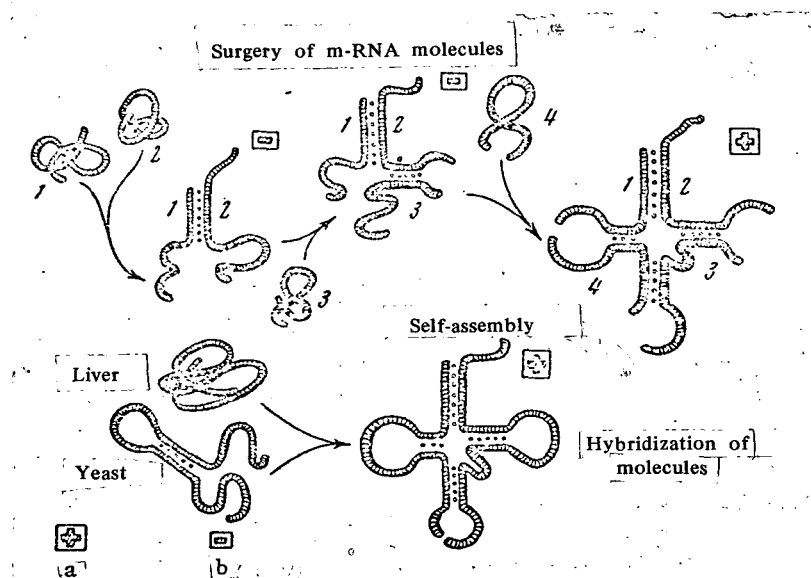


Figure 5. "Cut Molecule" of Valine Transfer RNA and RNA and Self-Assembly of Fragments: a) Active; b) Inactive Molecules.

this molecule must be able to fulfill extremely strict requirements in regard to its primary chemical structure. Parts of this whole, considered separately, are deprived of these properties but contain such extensive and accurate integrative information that, upon reacting with each other, these parts are able to achieve the same precise mutual arrangement as the one effected, under normal natural conditions, by the strictly prescribed presence of main-valence bonds. This fact also proves the presence of a most rigorous location of integrative forces within a protomer particle, which uniquely determines in advance the nature of the order that must emerge after integration takes place. This case can be considered particularly valuable and as if it were specially created to allow a study of integration phenomena and its accompanying laws on hand of an object of utmost simplicity.

Mention of these experiments has brought us close to that broad area in which the most varied and important information on the fundamentals of biological integration is being gathered at the present time. This area includes phenomena concerned with the so-called self-assembly, i.e. the formation of complex wholes from a mixture of their components, a process which takes place in an arbitrary manner. There are good reasons to assume that it is precisely in this area that the principle of integration will find a concrete expression in the development of biology of the near future.

Phenomena involving the arbitrary association of molecules, upon which self-assembly is based, attract a great deal of attention at the present time. As proof of this fact we can cite special symposia devoted to this problem, as well as the published works of these symposia. If we start from the most simple conditions, leaving aside the example just described of self-assembly from fragments of a molecule (which represents a narrowly special and particular case), then we must consider as the most descriptive that type of polymolecular association, in which association takes place between molecules of the same type.

In the field of nucleic acids, a well-known example of such a type of association is, naturally, the dual-strand helical structure of DNA. Two mutually complementary main-valence polynucleotide chains, arranged in anti-parallel manner, form a rigorously fixed helical structure ("double helix"). Two components are held in the prescribed conformation by numerous forces of weak interaction, primarily by means of hydrogen bonds, but also by means of other near-acting forces such as hydrophobic forces, etc.

The tendency towards intermolecular association is observed on a wide scale among proteins. A classical example is the hemoglobin molecule, which has the structure of a tetramer, i.e. a complex or association of four protomers—two alpha-polypeptide chains and two beta-chains.

The tendency towards association is expressed in an extremely marked degree in the case of enzymes. Recent investigations have established beyond doubt the remarkable fact that the great majority of enzymes is built up from subunits. Only a small number of enzymes, mostly those found in the form of single protein molecules, i.e. they represent a single polypeptide chain and are true monomers. Practically all other enzymes, which have been studied in greater detail in this respect, are built up from a certain number of subunits. The number of subunits in the active complex varies within wide limits in different cases. As a rule, this number is always an even number, thus showing that elements with a definite symmetry are present in the structure of the complex formed. Frequently, two or four subunits, i.e. dimers or tetramers, are found, but sometimes the number of subunits, i.e. protomers, is very high, up to 96 in the extreme case known so far. In the course of research now in progress in the Soviet Union, a subunit structure of aspartate transaminase was established by O. Polyanovsky working in the laboratory of Academician A.E. Braunshtein. In our laboratory, L. Kiselev and A. Parin reached the same conclusion with respect to one of the enzymes (amino acyl-t-RNA-synthetase, or "codase") binding amino acids, which must be used in protein biosynthesis, to the corresponding transfer nucleic acid carrying a specific encoding nucleotide triplet. Thus, the amino acid is provided with its own individual code label. Here, the following fact is important: these enzymes are bifunctional and perform two chemical acts; first, they activate the amino acid, and, second, they bind this acid to the nucleic acid. On the basis of data available to us, we can assume that these two functions are distributed among two subunits taking part in the build up of the enzyme particle. Thus, we believe that two types of integration are in effect here: a purely physical integration, in the sense of a union of two different protein molecules to form a discrete dimer, is accompanied by a functional integration. /816

The forces responsible for the association of molecules, including those responsible for self-assembly phenomena being discussed here, have already been mentioned. It must be emphasized that integration in the form of self-assembly at all levels of interest to us here is characterized by a strict order. Association of some random number of protomers never takes place, but combination always occurs between a number of protomers strictly prescribed in advance, whereby these protomers form a discrete whole endowed with a physical order defined as an arrangement of parts in space. At the same time, a functional integration of an equally high order also takes place. As an example we can cite the structure of the enzyme taking part in the conversions of pyruvic acid. The nucleus of this

enzyme consists of four pairs of trimers, each containing three subunits; these trimers form a cubic structure. Then, new protomers are attached to the eight corners of the cube, followed by attachment along the edges and the six faces of the cube. The final result is the formation of a giant particle with a molecular weight of about 4,500,000, consisting of 96 subunits. The most remarkable fact in this connection is that such a highly complex structure can arise quite spontaneously from an artificially formed mixture of separate components. Clearly, we can witness here precisely the distinct effect of integrative information, which predetermines in an unequivocal and compulsory manner the location (arrangement) of each component part making up the emerging whole.

As we have stressed above, the basis of integrative information, at least at those levels discussed here, consists in the sum total of forces of the weak interaction arising between atoms located in different sectors within one molecule or in different molecules. These forces exert their effect over very short distances, and for this reason are called short-range forces. As a rule, these distances do not exceed 4 Å. In order for these forces to exert their effect a very strict location in space is required from those atom groups which carry these forces. In essence, if extensive information were available on the nature and spatial arrangement of corresponding sources of weak interaction forces, it would be possible, by means of appropriate calculations, to predict the final result of their summary integral action. Of decisive importance in this case would be the requirement that this result should correspond to the minimum free energy of the system. This is an enormously difficult task, but one which in principle can be solved.

The possibility of making such predictions would be of exceptionally great significance in establishing the laws of biological integration. Undoubtedly, the most convincing criterion of the heuristic value of scientific understanding must be considered as the possibility, on the basis of this criterion, to make certain predictions which could be verified experimentally. Already certain signs point out that some cases are known, in which the above requirement can be fulfilled to a certain extent with respect to biological integration. This refers to the integrative information enclosed in the primary structure of the polypeptide chain of a protein molecule.

It is known that the primary structure determines the spatial three-dimensional configuration assumed by a macromolecule. Reports are available showing that, if the necessary information on parameters of the primary structure is fed into a powerful electronic computer, a graphic image of the tertiary structure, reflecting the order in which amino acid residues are arranged in the corresponding polypeptide chain, can be obtained on the screen of an oscillograph connected to the output of the electronic computer. A remarkable fact is that in some cases the answer supplied by the computer reproduced with a high degree of accuracy the space configuration (for example, of myoglobin) established by direct methods on the basis of an X-ray diffraction analysis. /817

Additional studies are required before a final judgement can be made on the reliability and authenticity of the results obtained, but in any case the search for possibilities of making predictions in this special field of integrative information is highly tantalizing. It is noteworthy that this problem is beginning to attract

increasing attention. Anfinsen (1967) has devoted a special section in his monographic review to the problem concerned with predictions of arising structures. Work in this direction is also in progress at the Protein Institute in Pushchino (under the direction of O.B. Ptitsyn).

As was mentioned previously, the effect exerted by weak forces taking part in integration phenomena at the molecular level extends over a distance not greater than 4 \AA . For this reason, information telling us what regions of the molecular structure, taking part in the association of protomers, may be spatially located so close to each other that short-range forces can exert their effect between them will be of decisive importance in establishing the rules operating in various forms of integration, and specifically in the case of macromolecular association. Undoubtedly, proteins will play a leading role as objects of such a type of investigation. In this connection, it is a tempting thought to visualize, in the same way as in the field of nucleic acids the alphabet of the nucleotide language has been deciphered in the past 10 years, that also in the field of interactions involving proteins it will possibly in due time come close to an understanding of the amino acid language with its 20-letter alphabet. Specific groups of amino acid residues in the polypeptide chain could possibly act as "words" in this language. The work of Perutz (1969) represents a very interesting start for such an approach and for making the first few steps in this direction. On the basis of the three-dimensional structure of hemoglobin which he obtained, and with a resolution of about 2 \AA , Perutz was able to determine which amino acid residues in the alpha- and beta-chains are present in a Van der Waals contact, i.e. at a distance of less than 4 \AA from each other. The data obtained by him are shown in a table (see below), which is drawn on the basis of a somewhat different principle than the one used by Perutz for his graph. This table indicates, for each amino acid, with which other (or the same, but located in a different spot) amino acid residues the given amino acid is "in contact". At this time, it is not possible yet to state that some clearcut rules are becoming outlined. To reach this goal much more extensive material will have to be available, and preferably data referring to different types of protein. Obviously, it would be a tremendous achievement if we could find some "molecular Rossetta Stone", i.e., a particularly favorable object, with the help of which, as was done with DNA in the nucleotide language area, it would be easier to undertake the deciphering of the immeasurably more complex "amino acid language".

The excellent mode of action of integrative information, manifested in the association and self-assembly of protein formations, is no longer a source of surprise to us, since we are already familiar with examples in which problems of an even more complex order are solved on the basis of this principle. These examples include numerous and varied cases, where complex wholes are formed as a result of a mutual integrative consolidation of component parts, which do not belong to the same class of chemical compounds, as was the case in the examples mentioned above; rather, a whole (integral) system of a higher level arises, which is built up from component parts having a different (heterogenous chemical nature). We are mainly concerned here with protein compounds and nucleic acids.

From a strictly chemical viewpoint these are products which could be formally classified as nucleo-proteides. However, from a biological standpoint we are confronted here with an exceedingly large and varied group of formations with different biological character.

TABLE: CONTACTS BETWEEN AMINO ACIDS IN THE HEMOGLOBIN MOLECULE

I	II
Ala ^c	Val, Leu, Gly, Val, Ser
Arg	His, <u>Gln</u> , Pro, Thre, Phen, Pro, Val, Threa, Tyr, Leu, Arg, Try, <u>Asn</u> , Phen
Asp	Tyr, Val, Try, <u>Asn</u>
<u>Asn</u>	His, Asp
Val	Gly, Arg, Leu, Ala, Asp, Try, Asp, Gly, Thre
His	<u>Gln</u> , Leu, Asn, Thre, Thre, Arg
Gly	<u>Gln</u> , Ala, Val
Glu	Pro, Val
Gln	Gly, His, Arg, Cys, Ser, Arg
Iso-leu	- - - - -
Leu	Ala, Glu, Pro, His, Ser, His, Arg
Met	Pro
Pro	Met, Pro, Val, Thre, Tyr, Glu, <u>leu</u> Pro, Arg
Ser	<u>Gln</u> , Ala, Leu
Tyr	Asp, Arg, Pro, Tyr
Thre	Arg, His, Val
Try	Arg, Val, Pro, Try
Phen	<u>Gln</u> , Arg, Leu, Val
Cys	<u>Gln</u>

In column I are listed individual amino acids present in the alpha- and beta-chains of hemoglobin. In column II are listed those amino acids present in other sectors of the chains, with which the given amino acid is in contact, i.e. at a distance of less than 4 Å.

If we also start here from the most simple type of structure and the most primitive biological function, then we see that the compounds most closely related to nucleoproteides from a chemical standpoint are complexes formed between proteins and those ribonucleic acids which carry genetic information from the chromosome apparatus of the cellular nucleus to cytoplasm ribosomes. These are the so-called information, or matrix, ribonucleic acids. A.S. Spirin (1968) found in the cytoplasm discrete particles called informosomes and consisting of a protein and a nucleic acid. After being isolated by appropriate physical methods, these informosomes exhibited constant physical parameters and a constant ratio of their component parts, which made it possible to consider them as functional individuals. In the cellular nucleus (Georgiev, Samarina, 1969) particles were found, which were built up from the same components and were called informopheres; they took part in the transfer of matrix ribonucleic acid from the location where it was formed, i.e. from DNA molecules in the chromosomes to the nucleus-cytoplasm boundary. Informopheres could be described in detail, both on a morphological plane under the electron microscope and in regard to their chemical composition and properties. It is particularly important to note the ability of informophere particles to take part in self-assembly phenomena. Under appropriate conditions, the protein and nucleic acid can be separated from each other and obtained in the form of separate products, while upon mixing both components they again join to form particles having the previous composition and properties. The ability to undergo self-assembly, with a restoration of the previous type of order,

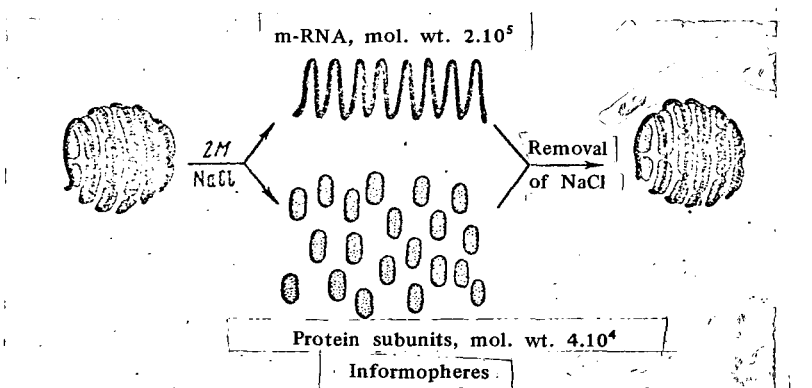


Figure 6. Structure of an Informophere Particle, Breakdown and Self-Assembly.

indicates that we are dealing here with an integration process, with a guided (directed) action of the integrative information found in the properties of component parts, which interact and form a new entity (unity).

Probably, the discovery of this type of phenomena in connection with tobacco mosaic virus represents one of the earliest examples of self-assembly in the field of biological macromolecules. The general structural scheme of a molecule of this virus is well known to everybody. The structure consists of an RNA strand forming a helix with a diameter of 80\AA containing 6300 nucleotides in each molecule. Protein subunits (2130 per molecule) are strung on this helix; in other words, in a ratio of 1 protein subunit for each 3 nucleotides in the RNA strand.

We are interested only in one fact. By appropriate methods it is possible to separate the protein from the nucleic acid and to obtain each component in the form of an individual chemical product. When both components are mixed a complete regeneration of the original virus particle is achieved, with restoration of all its physical parameters and its specific biological properties, namely the infection capacity of the virus. A complete reintegration takes place: from two separate components something entirely new emerges, namely a virus particle endowed with all its values. We can easily grasp how great must be the perfection of the integrative information recorded in the properties of the protein and nucleic acid molecules, which makes it possible to achieve such an accurate reconstruction. One is involuntarily struck by the notice, recorded in some mysterious way, that the process of self-assembly should stop at the moment when precisely 2130 protein subunits, and not 2129 or 2140 subunits, become attached to the RNA strand.

The same high degree of reliability of integrative information is also manifested in all other cases in which it was possible to establish the presence of self-assembly phenomena in a wide variety of other virus types. The number of such examples is very great, and we have all reasons to believe that this represents a quite universal and general conformity with a law. And we must remember that the structure of tobacco mosaic virus is perhaps one of the most simple structures found among all other viruses. Very high degrees of order are observed in the entire broad group of viruses of the spherical or isometric type, where an icosahedron type is the most frequent basis of the structure and where structural details of the virus particle are uniquely prescribed by symmetry laws. These

laws, together with various previously mentioned forces of intermolecular reactions, or, more precisely, in close union with these forces, must be considered as an important category of those factors making up integrative integration.

The above example showing self-assembly of the tobacco mosaic virus is the earliest one among known cases of manifestation of integrative information in self-assembly phenomena. This virus belongs to a number of very large-sized viruses. Quite recently, information has been obtained, concerning self-assembly phenomena taking place in one of the viruses having the smallest size, namely in bacteriophages of a very simple structure (phages of type R17 and Q β). These phages consist on a single-strand RNA molecule containing only 3 genes. These genes effect the synthesis of three proteins. The first one is the protein forming the sheath of the virus particle. The second is a protein with enzyme properties, RNA replicase, which effects the self-reproduction of RNA when the virus multiplies. The third protein has a special mission: it controls the self-assembly of the virus particle from a mixture of its components. We even know the order in which these genes are located in the RNA chain: first, the "self-assembly" protein, then the sheath protein, then the enzyme protein (replicase). If RNA and the above 3 proteins are mixed in a test tube, these components assemble spontaneously and form a highly specific structure, which corresponds to a virus particle fully endowed with its properties.

This example can serve, first, to demonstrate how deeply modern research delves into the inner mystery of viral structure; second, we can see that in some cases we must attribute to definite components of a biological whole (entity) a specialized function, which makes it possible to achieve the required order during the process of self-assembly. To a certain extent we have here an example of integrative information of the type designated above as "directive" information, when we were talking about matrix synthesis.

Ribosomes, these molecular factories of protein biosynthesis, represent biological formations with particularly broad, general biological functions and an extraordinarily perfect, highly complex structure (Fig. 7). From the standpoint of integration phenomena and the role played by integrative information, ribosomes are of exceptional interest. A ribosome consists of two half-sections: a light one, with a sedimentation constant of 30S, and a heavy one, with a sedimentation constant of 50S. Their chemical composition includes one nucleic acid (of very high molecular weight) in each half-section and a large number of proteins. The number of individual polypeptide chains is of the order of one hundred, and several dozen different proteins are present. In spite of this extreme complexity and the high order of their structure, it was possible to breakdown ribosomes into their components parts, and from these the entire highly complex structure can be rebuilt again as a result of self-assembly. This has been demonstrated by A. Spirin with respect to the dissociation of ribosomes into half-sections and the step-by-step removal of various amounts of protein, after which self-assembly could take place upon creating favorable conditions, leading all the way to the formation of normal ribosomes fully endowed

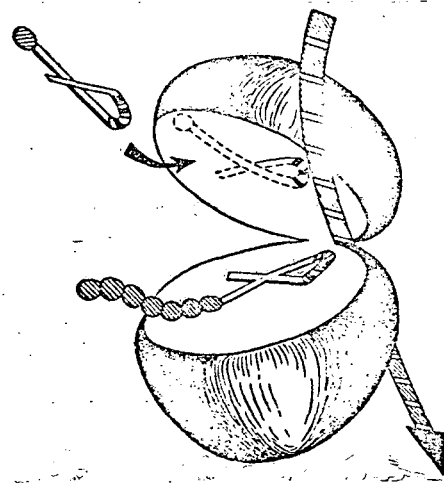


Figure 7. Structure Diagram of a Ribosome.

with their own properties. Recently, Nomura (1969) succeeded, by working with one ribosome half-section, in carrying out the process of breakdown and subsequent self-assembly still further, namely to the point of complete protein removal and restoration of the normal biological activity after self-assembly.

In regard to the level of complexity of the biological whole (entity) formed in this case, these results represent today the highest achievement on the road leading to an understanding of biological integration. We can already visualize mentally how the experimental research worker will be able to breakdown mitochondria into their components, and how, from these parts, he can again assemble these "power plants" of cellular power engineering under the invisible directions of integrative information. And, finally, as the apex of triumph, we can imagine that under appropriate conditions the researcher will witness the appearance, from a disorderly mixture of components, of "synthetic" chromosomes, formed from unwound DNA strands and added histones as a result of self-assembly, i.e. by means of integration at a supermolecular level, in a manner similar to what takes place in the cell nucleus during mitosis.

Integratism is not a goal but a path. The guarantee of a correct combination and an adequate ratio between reductionism and integratism is the basis of the strategy for scientific research in understanding life phenomena within the near future, and, more correctly, the basis of the entire future growth of biology as an exact science. In this connection, the leading principle must consist in an attempt to construct schemes and concepts of integratism, using as a starting point data obtained along the course followed by reductionism, i.e. starting from the most simple and elementary conditions to go up step by step along the rising stages of hierarchical gradation, switching to the steadily increasing degrees of complexity of the systems under investigation.

We should not be blind to the fact that, at the present time and at the present level of development of integratism, we are forced to operate predominately with information of a phenomenological character. Knowledge of deeper motive forces, details of their action mechanisms and causal and functional aspects still remain hidden to a large extent. Overcoming these gaps must be the object of the most important sectors in biological research, aimed at the elucidation of basic and fundamental problems arising in the study of the nature of life problems.

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Translated for the National Aeronautics and Space Administration by
Scripta Technica, Inc. NASW-2036.